Medical and Pediatric Oncology 28:420–423 (1997)

Bilaterally Multicentric Synchronous Wilms' Tumor: Successful Conservative Treatment Despite Persistence of Nephrogenic Rests

Jacinto J. Regalado, MD,[1] Maria M. Rodriguez, MD,[1]* and Stuart Toledano, MD[2]

We report a case of synchronous bilateral Wilms' tumor in a girl with incomplete Beckwith-Wiedemann syndrome and hemihypertrophy. Multiple small tumors were present in both kidneys. The initial diagnostic biopsy showed stage I monophasic blastematous Wilms' tumor of favorable histology, with multiple perilobar nephrogenic rests (nephroblastomatosis). By flow cytometry, tumor was diploid, with an S-phase fraction of 13.9%. Dactinomycin and vincristine were begun as per the National Wilms' Tumor Study IV (18 week course). After 1 month, only a single small lesion was evident, which persisted unchanged. Excisional biopsy 5 months after beginning chemotherapy showed entirely necrotic tumor but apparently unaltered nephrogenic rests. After completing chemotherapy, the child has done well, with normal renal function and no evidence of disease 3 years after diagnosis. Management of stage V Wilms' tumor is tailored to the individual case, being as conservative as possible to spare renal parenchyma. Given the high incidence of coexisting nephrogenic rests in bilateral Wilms' tumor, careful follow-up is required, as these potentially premalignant rests may resist chemotherapy. Med. Pediatr. Oncol. 28:420–423, 1997.

Key words: Beckwith-Wiedemann syndrome; hemihypertrophy; nephroblastomatosis; nephrogenic rests; nephromegaly; Wilms' tumor

INTRODUCTION

The earliest confirmed case of Wilms' tumor (WT), predating Max Wilms' classic 1899 monograph by more than a century, involved both kidneys simultaneously [1]. However, only about 6% of WTs are bilateral and synchronous [2].

Such cases are more common in females [3,4], and the median age at diagnosis (30.5 months for females, 23.5 months for males) is about 1 year less than that for unilateral WT in both sexes [3]. About 25% of bilateral cases are associated with at least one congenital anomaly (especially urogenital defects and hemihypertrophy); this is twice the incidence found in unilateral WT [5]. Virtually all bilateral WTs reveal associated nephroblastomatosis, defined as the presence of multiple nephrogenic rests (NR) [6]. These rests are usually perilobar (PLNR) in synchronous cases [6].

The three main prognostic factors are histologic type (favorable or unfavorable), most advanced local stage, and age at presentation [2]. About 10% of stage V cases show unfavorable histology (anaplasia) and have a 20% 5 year survival [2]. Substages I and II do much better than higher ones, and children below age 3 years do much better than those 4 years or older [2]. Overall 10 year survival is 70–80% [2,4].

Therapy must be individualized and varies according to the circumstances; the guiding principle is to conserve as much renal parenchyma as possible. We present a bilaterally multicentric WT with NR treated successfully with biopsy and subsequent chemotherapy only. The apparent resistance of the NR to conventional adjuvant therapy is also discussed.

CASE REPORT

A white Latin girl was found to have bilateral renomegaly by prenatal ultrasound, with normal amniotic fluid volume. Delivered at 38 weeks, she weighed 6.5 lb. The initial diagnosis was autosomal recessive (infantile) polycystic kidney disease, later revised to autosomal dominant (adult type). There was no family history of renal disease, although the mother reportedly had asymmetric kidneys. Both parents were in their twenties.

At 2 months, the baby presented with Caffey's disease (infantile cortical hyperostosis) of the mandible and scapular bones, a typically self-limiting inflammatory bone disorder. A large tongue and a small umbilical hernia were noted. Both kidneys were palpable. Ultrasound showed enlarged kidneys with normal texture and with-

[1]Department of Pathology, Division of Pediatric Pathology, Jackson Memorial Medical Center, University of Miami School of Medicine, Miami, Florida; [2]Department of Pediatrics, Division of Hematology and Oncology, Jackson Memorial Medical Center, University of Miami School of Medicine, Miami, Florida.

*Correspondence to: Dr. Maria M. Rodriguez, Department of Pathology (D-33), University of Miami School of Medicine, P.O. Box 016960, Miami, FL 33101.

Received 24 June 1996; Accepted 26 September 1996

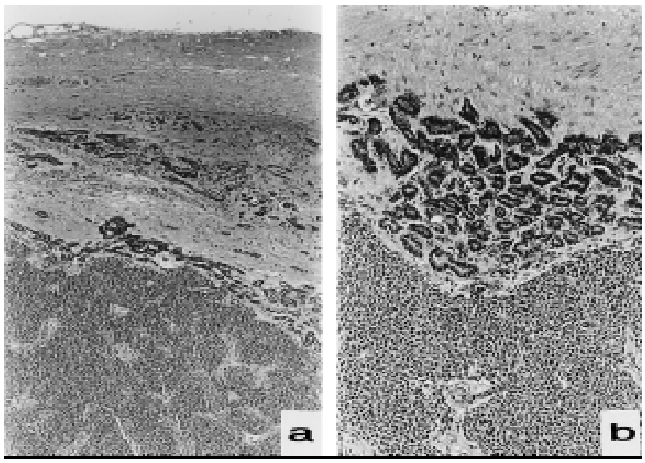

Fig. 1. **a:** *Bottom to top:* Nodule of blastema, rim of tubular rests, fibrous pseudocapsule, outer layer of sclerosing rests, and renal capsule. Hematoxylin-eosin, ×100. **b:** Sharply demarcated tumor blastema with adjacent embryonal rest tubules and intrarenal pseudocapsule. Hematoxylin-eosin, ×200.

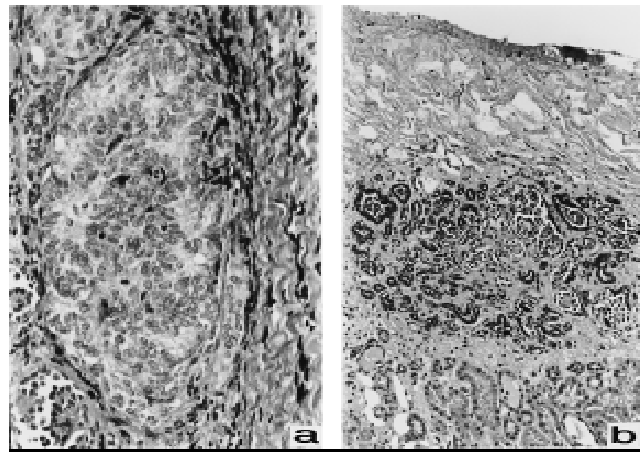

Fig. 2. **a:** Ovoid hyperplastic NR, taking up most of the field. Masson trichrome, ×400. **b:** *Top to bottom:* Renal capsule, sclerosing perilobar rest (note hyperchromasia), and mature renal tubules. Hematoxylin-eosin, ×200.

out cysts, duplication, or hydronephrosis. Renal scan indicated delayed excretion with cortical retention, but serum markers of renal function were within normal limits.

The child did well until 2.5 years of age, when she presented with pyelonephritis due to an *Escherichia coli* urinary infection. Blood urea nitrogen and creatinine were normal. Various imaging studies showed mildly enlarged kidneys with bilateral round, solid lesions, 1–2 cm each. Depending on imaging modality, each kidney showed one or two masses. Concurrently, mild hemihypertrophy was noted involving the right lower extremity.

At laparotomy, the left kidney surface showed 8 white and firm round nodules, each about 1 cm. Two nodules were excised; frozen section diagnosis was in situ WT without anaplasia. No adenopathy was noted; the right kidney was not explored. Three days later, computed tomographic (CT) scan with contrast (not employed in the preoperative CT) showed multiple round, low-density lesions, up to 1.5 cm, scattered over both kidneys peripherally. Several lower periaortic lymph nodes under 1 cm were noted, interpreted as likely postoperative effect. The spleen was somewhat enlarged (8.5 cm). No other visceral or soft tissue abnormalities were visualized.

Histologic examination of the biopsy specimen showed two round and discrete subcapsular nodules, 0.7 and 1.0 cm, respectively, composed of blastema with an organoid pattern. Mitoses were frequent but not multipolar; no anaplastic nuclei were found. Each nodule had a peripheral rim of embryonal tubules typical of sclerosing PLNR. This rest layer was covered in turn by a fibrous intrarenal pseudocapsule, immediately beyond which were additional PLNR (Fig. 1). The latter were mostly of the sclerosing type, but a few hyperplastic rests were noted (Fig. 2a). Sclerosing PLNR were also present below the renal capsule away from the WT nodules (Fig. 2b). The uninvolved renal tissue revealed uniformly large glomeruli that nearly filled Bowman's spaces, and also small foci of tubulo-interstitial dysplasia.

Flow cytometric DNA analysis of formalin-fixed, paraffin-embedded WT revealed a uniformly diploid population with DNA index of 1.0 and synthetic (S)-phase fraction of 13.94%.

Chemotherapy was begun with pulsed dactinomycin and vincristine (18 week course), as per the National Wilms' Tumor Study (NWTS) IV for stage I cases. One month later, renal sonogram showed normal-sized kidneys and only one apparent nodule. After 2 months of therapy, sonogram showed no definite renal lesions and a clear inferior vena cava; CT with contrast revealed one nodule in the left kidney. After 4 months of treatment, sonogram also showed a left-sided nodule. Chest imaging showed no lung lesions. After 5 months, CT scan still suggested a vague nodule in the left upper kidney, prompting an open biopsy.

At surgery, a white lesion, less than 1 cm and flush with the kidney surface, was found in the area in question and excised. No other lesions were seen; the right kidney was not explored. Histologic analysis showed a round 0.6 cm nodule, with a central core of entirely necrotic tumor surrounded by a thick fibrous collar. Viable sclerosing PLNR were present at the periphery of the lesion and below the renal capsule. These rests (Fig. 3) appeared unchanged from those seen in the initial biopsy. No hyperplastic NR, however, were identified in the new material.

The child has done well after completing chemotherapy; her renal function has remained normal. She has been followed closely with regular clinic visits and quarterly abdominal sonograms, which have shown no evidence of disease since her last surgery. It is now 3 years since her WT was diagnosed.

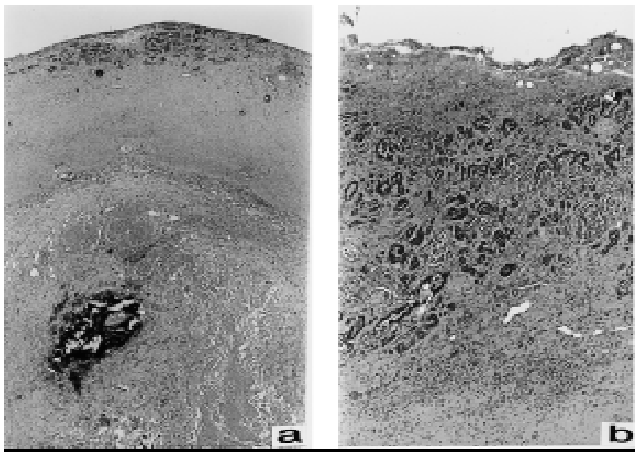

Fig. 3. **a:** *Bottom to top:* Necrotic tumor nodule with focal dystrophic calcification (black area), thick fibrous collar, and outer rest layer just below renal capsule. Hematoxylin-eosin, ×40. **b:** Viable subcapsular sclerosing rests (compare to prechemotherapy picture, Fig. 2b). Hematoxylin-eosin, ×100.

DISCUSSION

Points of special interest in this case of synchronous bilateral and multicentric WT are the associated congenital anomalies, the management approach, and the fate of the NR.

The child had a history of renomegaly, macroglossia, umbilical hernia, splenomegaly, and hemihypertrophy (Hh). She also had large glomeruli and focal renal dysplasia. This constellation indicates a form of Beckwith-Wiedemann syndrome (BWS), which can be incompletely expressed clinically and lacks a consistent phenotypic marker [7]. A classic BWS stigma, macrosomia, was absent, but this is only seen in about 40% of cases [7]. Significantly, incomplete BWS variants have the same oncogenic potential as classic BWS, about 8% [8]. Hemihypertrophy is seen in 12% of BWS cases, but up to 50% of those cases develop WT, as if by synergy of the two anomalies [8,9].

Clinically, Hh can be rather subtle. It may not affect an entire side, and isolated leg involvement is the most common manifestation [8]. In one large series, only one third of WT/Hh cases had the Hh diagnosed before the tumor [8].

The approach to stage V WT has become progressively more conservative to spare renal units. There appears to be increased risk of late renal dysfunction if >50% of renal tissue is removed [10]. There is no difference in survival between initial tumor resection and initial biopsy followed by chemotherapy and subsequent surgery [11]. Initial resection is no longer recommended; the preferred sequence is biopsy, chemotherapy, and then resection using bilateral renal-sparing procedures whenever feasible [12]. The biopsy not only confirms the diagnosis of WT, but also helps establish local tumor stage and favorable vs. unfavorable histology (although the latter may be missed by sampling error). Chemotherapy is meant to ''shrink'' the tumor to facilitate surgery, arrest tumor growth to protect kidneys from enlarging-mass effects, and reduce or ablate WT precursor cells in NR that might undergo neoplastic induction [13]. If the preresection tumor response is insufficient, different chemotherapy or radiation or both may be employed [12]. If tumor response remains inadequate for renal salvage, radical nephrectomy is performed; bilateral nephrectomy is a last resort.

Until recently, less than 5% of stage V cases have been handled with biopsy, chemotherapy ± radiation, and no further surgery; about 95% of cases have had an initial or subsequent resection [2]. In the current case, there were multiple small, superficial WTs in both kidneys. Conceivably, at least if there had been fewer lesions, they could have been managed with local resection alone. However, such tumors may be ''sterilized'' by chemotherapy, which is what happened here based on the second biopsy and follow-up sonograms. The need for that second biopsy is debatable, as the lesion in question had persisted unchanged and could have been followed radiographically [13], but parental anxiety precluded the conservative course.

Tumors that respond so well (<10% viable tumor left after chemotherapy) have excellent prognosis regardless of stage (>90% disease-free survival), though the supporting data consist of unilateral cases which eventually had resection [14]. In our case, it is possible that viable tumor cells were left in non-biopsied sites, or that new tumor could develop from the remaining PLNR. Most deaths (76%) in stage V patients are due to progressive disease, and most of these tumor deaths occur within 2 years of diagnosis [2]. Consequently, radiographic surveillance is mandatory. Bruce Beckwith, NWTS pathologist, recommends quarterly ultrasounds for the first 2 years, with continuing surveillance until about age 8 years, for children with BWS or other conditions with PLNR, such as isolated Hh (Beckwith, personal communication). By that time, he adds, about 95% of WTs in this population will have been diagnosed.

An interesting parallel to our case is one described by Haddy et al. [15] and Kulkarni et al. [16]. They report a girl with BWS and Hh who developed bilateral superficial diffuse nephroblastomatosis, treated with a 15 month course of actinomycin D and vincristine. There was good clinical response and postchemotherapy biopsies showed marked reduction in NR, as well as evidence of maturation in the NR that remained. However, 2 years later, the child presented with a right WT, which was resected with intraoperative rupture. A left kidney biopsy showed residual NR. She received three-agent chemotherapy and radiation, and apparently did well subsequently.

In the setting of WT (unilateral or bilateral) accom-

panied by NR, the rests are typically bilateral [13], so even if all tumor is removed, any remaining ''normal'' kidney is at some risk for subsequent WT. It is not known to what extent chemotherapy given for WT ablates or deactivates associated NR. There is a paucity of published data on the subject, though Beckwith has noted that NR remnants may be found in postchemotherapy specimens and that such remnants are usually sclerosing or hyperplastic NR without mitotically active blastema [13]. As graphically shown in the present case, despite excellent tumor response, NR can remain untouched by adjuvant therapy, at least at the light microscopic level (we have seen the same phenomenon in unilateral WT). We cannot speak for changes at the molecular level, which may be the key issue. Our patient has been disease-free 3 years since diagnosis and is presumably cured, but besides the Haddy et al. case there are uncommon cases of WT with NR that develop metachronous contralateral tumor after chemotherapy. The implication, of course, is that conventional adjuvant therapy does not always prevent neoplastic transformation of NR. The relationship between NR, chemotherapy, and the risk of subsequent *de novo* WT requires additional study.

The role of flow cytometry as a prognostic tool for WT is not well established. In some series, most cases were diploid, and aneuploidy and high DNA index were associated with anaplastic tumors [17]. The latter also tended to show higher proliferative rate as indicated by S-phase fraction (median fraction of 20% vs. 13.6% for favorable histology) [17]. Other series, however, have found most WTs to be aneuploid, with no significant relationship between ploidy and survival [18]. Further investigation in this area may prove useful.

ACKNOWLEDGMENTS

The authors thank Dr. Bruce Beckwith of the NWTS for his expert opinion on this case as well as his instructive comments on other cases we have sent him in consultation.

REFERENCES

1. Beckwith JB: Wilms' tumor and other renal tumors of childhood: An update. J Urol 136:320–324, 1986.
2. Montgomery BT, Kelalis PP, Blute ML, Bergstralh EJ, Beckwith JB, Norkool P, Green DM, D'Angio GJ: Extended follow-up of bilateral Wilms' tumor: Results of the National Wilms' Tumor Study. J Urol 146:514–518, 1991.
3. Breslow N, Beckwith JB, Ciol M, Sharples K: Age distribution of Wilms' tumor: Report from the National Wilms' Tumor Study. Cancer Res 48:1653–1657, 1988.
4. Coppes MJ, de Kraker J, van Dijken PJ, Perry HJM, Delemarre JFM, Tournade MF, Lemerle J, Voute PA: Bilateral Wilms' tumor: Long-term survival and some epidemiological features. J Clin Oncol 7:310–315, 1989.
5. Breslow NE, Beckwith JB: Epidemiological features of Wilms' tumor: Results of the National Wilms' Tumor Study. J Natl Cancer Inst 68:429–436, 1982.
6. Beckwith JB, Kiviat NB, Bonadio JF: Nephrogenic rests, nephroblastomatosis and the pathogenesis of Wilms' tumor. Pediatr Pathol 10:1–36, 1990.
7. Sotelo-Avila C, Gonzalez-Crussi F, Fowler JW: Complete and incomplete forms of Beckwith-Wiedemann syndrome: Their oncogenic potential. J Pediatr 96:47–50, 1980.
8. Green DM, Breslow NE, Beckwith JB, Norkool P: Screening of children with hemihypertrophy, aniridia, and Beckwith-Wiedemann syndrome in patients with Wilms' tumor. Med Pediatr Oncol 21:188–192, 1993.
9. Wiedemann HR: Tumours and hemihypertrophy associated with Wiedemann-Beckwith syndrome (letter). Eur J Pediatr 141:129, 1983.
10. Ritchey ML, Green DM, Thomas PRM, Smith GR, Haase G, Shochat S, Moksness J, Breslow NE: Renal failure in Wilms' tumor patients: A report from the National Wilms' Tumor Study Group. Med Pediatr Oncol 26:75–80, 1996.
11. Shaul DB, Srikanth MM, Ortega JA, Mahour GH: Treatment of bilateral Wilms' tumor: Comparison of initial biopsy and chemotherapy to initial surgical resection in the preservation of renal mass and function. J Pediatr Surg 27:1009–1015, 1992.
12. Ritchey ML, Coppes MJ: The management of synchronous bilateral Wilms' tumor. Hematol Oncol Clin North Am 9(6):1303–1315, 1995.
13. Beckwith JB: Precursor lesions of Wilms' tumor: Clinical and biological implications. Med Pediatr Oncol 21:158–168, 1993.
14. Zuppan CW, Beckwith JB, Weeks DA, Luckey DW, Pringle KC: The effect of preoperative therapy on the histologic features of Wilms' tumor. Cancer 68:385–394, 1991.
15. Haddy TB, Bailie MD, Bernstein J, Kaufman DB, Rous SN: Bilateral, diffuse nephroblastomatosis: Report of a case managed with chemotherapy. J Pediatr 90:784–786, 1977.
16. Kulkarni R, Bailie MD, Bernstein J, Newton B: Progression of nephroblastomatosis to Wilms' tumor. J Pediatr 96:178, 1980.
17. Douglass EC, Look AT, Webber B, Parham D, Wilimas JA, Green AA, Roberson PK: Hyperdiploidy and chromosomal rearrangements define the anaplastic variant of Wilms' tumor. J Clin Oncol 4:975–981, 1986.
18. Layfield LJ, Ritchie AW, Ehrlich R: The relationship of deoxyribonucleic acid content to conventional prognostic factors in Wilms' tumor. J Urol 142:1040–1043, 1989.